

B2 cond'd. 16-58. A composition according to claim ¹⁷ 57 in which two or more fluorochromes are incorporated into each subrange of microparticles.

IN THE TITLE

Amend the title to read "MAGNETIC PARTICLES AS SOLID PHASE FOR MULTIPLEX FLOW ASSAYS".

REMARKS

New claims 50-53 are supported in the Specification at p. 6. New claims 54-58 are supported in the specification at p. 8 line 8 through p. 10 line 31.

The title is objected to as not indicative of the claimed invention. The above amendment should be sufficient to overcome this objection.

Claims 21-29 are under examination in this application, and stand rejected under 35 U.S.C. 103 as obvious over the combination of Coulter (British patent 1,561,042) and Bibette et al (USP 5,245,964).

Claim 21 has been amended to state that the magnetic microparticles are suitable for use in a multiplex assay procedure that includes the use of flow cytometry. With respect to the cited art, Applicants further submit that (a) the two references are not combinable as such, for reasons discussed below, and (b) in any event, the above-mentioned distinction (which is supported by the overall specification) distinguishes the claimed compositions from any composition that is produced by a combination of the references.

Coulter discloses the use of particles having different size subranges in a multiplex assay. The particles, however, as recognized by the examiner, are not magnetic particles, and there is no disclosure in Coulter et al. that would indicate to those skilled in the art that magnetic particles could or should be used in the Coulter process.

Bibette et al. disclose a type of magnetic particle that can be used, inter alia, in immunoassays. However, the disclosure is very general, and does not indicate any particular type of assays in which these specific magnetic particles may be used, or

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any advantage they may have over other types of magnetic particles used in immunoassays. The essence of the Bibette et al. invention is the production of magnetic particles having a narrow size distribution from aqueous dispersions having a wider size distribution. There is nothing in this reference that in any way suggests that these particles may be useful in multiplex assays.

Neither of the references combines the teaching of the use of magnetic particles with the teaching of the multiplexing of immunoassays. The significance and nonobviousness of this combination however is not recognized in the Office Action. It is true, as the Action notes, that magnetic particles are known in general to be an effective means of separating a solid phase from a liquid phase, as disclosed, for example in Bibette et al.. In this invention, however, magnetic particles are not only separated from the liquid phase, but also are *differentiable and differentiated* from each other, and this is a critical distinction. As described in the specification, this requires *re-suspension* of the particles after the magnetic field has been applied and the use of *flow cytometry* on the resuspended particles. This, in turn, requires magnetic particles that are suitable for use in flow cytometry.

It is true that neither re-suspension nor flow cytometry is new *per se*. However, neither of these two features is present in single-assay protocols, and neither has been shown in the cited art to be applied to magnetic particles. Flow cytometry is a process that is sensitive to the composition of the particles and their interactions with each other. Adding a magnetic character to the particles can give the particles a strong interparticle attraction or repulsion (both of which can affect their ability to be resuspended). Adding a magnetically responsive component to the particle mass can seriously affect the properties of the particle. In the context of the present invention, magnetically responsive particles must do much more than simply offer a means to separate the particles from a liquid by placing a magnet nearby. The problems and risks that arise when resuspension and flow cytometry are applied to magnetic particles in a multiplex assay system, which were listed in Amendment No. 1, are neither recognized nor addressed in the prior art. Specifically:



None of the prior art on either flow cytometry or magnetized particles addresses the risk that magnetized particles will settle out before passing through the flow cytometry cell. Note that this risk is much greater with magnetic particles than it is with particles of latex, which is the traditional particle material used in flow cytometry.

None of the prior art on either flow cytometry or magnetized particles addresses the risk that magnetized particles upon resuspension will not completely separate and instead remain as aggregates that will clog the flow cell. Latex particles, such as are used in Coulter, which have much less a tendency to form aggregates, do not present this problem, nor do they present a risk of comparable magnitude.

None of the prior art on either flow cytometry or magnetized particles addresses the risk of losing magnetic character of having magnetic characters of widely varying magnitude that would interfere with the particles' ability to function uniformly as magnetic particles, when the particles are fabricated in different sizes or with different dyes or some other differentiation parameter.

The Examiner takes the position that it would be obvious to combine the two disclosures to provide a multiplex process using magnetic particles would be obvious, particularly since both references relate to particles having size subranges. However, to simply combine the teachings of the two references overlooks the above-mentioned complexities of seeking to adapt magnetic particles to a multiplex assay that includes flow cytometry. Additionally, each reference defines a complete process in and of itself, with no indication therein to suggest any such combination. From their disclosures, those skilled in the art would not be motivated to combine the two references. In addition, with the complexities mentioned above, those skilled in the art would not be taught from the references how to obtain a composition containing magnetic particles that are differentiable for use in a multiplex assay that includes flow cytometry.



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PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

21. (Amended) A composition comprising a plurality of solid-phase assay reagents selectively active in a plurality of assays each for a different analyte, each said solid-phase assay reagent comprising a binding species that is [selective] selectively active in a single assay and coupled to one of a plurality of microparticles of magnetically responsive material, the sizes of said microparticles varying in size over a range that is an aggregate of a plurality of subranges, each subrange distinguishable from other subranges of said aggregate by flow cytometry and by the binding species coupled thereto, said microparticles being suitable for use in a multiplex assay procedure that includes the use of flow cytometry.

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